Nicotinic receptors in brains of healthy individuals and Alzheimer patients as visualized in vivo by positron emission tomography and ^{11}C-methyl nicotine.

Agneta Nordberg

Department of Pharmacology,Uppsala University and Departement of Geriatric Medicine,Karolinska institute,Sweden.

Alzheimer´s disease is a progressive neurodegenerative disorder with global deterioration of cognitive function. Among the afflicted transmitter systems in brain the cholinergic system is the one that correlates best with cognitive function. Several postmortem studies now confirm the marked reduction in cortical nicotinic receptors density in Alzheimer´s disease. The decrease in nicotinic receptors has been confined to the biological active (S) enantiomer of nicotine. The results are based on material obtained at autopsy or by biopsy and have to be confirmed in vivo.

Attempts to visualize nicotinic receptors in vivo using ^{11}C-nicotine and positron emission tomography (PET) have recently been made in monkey and man. The aim of the present study was to assess by PET the use of (-) (S) nicotine labelled with ^{11}C as well as the enantiomer of nicotine, with lower receptor affinity, the (+) (R) form, as markers for nicotinic receptors and/ or unspecific disposition of ^{11}C-nicotine in brain of healthy volunteers and Alzheimer patients.

The nicotinic enantiomers (-)(S) and (+)(R) ^{11}C-nicotine was injected to six patients with the diagnosis Alzheimer´s disease (agen range 63-74,duration of disease 1-10 years) and six age matched healty volunteers.None of the subjects were smokers. The radioactivity from (+) and (-) ^{11}C-nicotine was rapidly distributed from arterial blood after i.v. injection. The radioactivity peaked in brain within 2-5 minutes and was then followed during 30 mins. The uptake of ^{11}C-nicotine in healthy volunteers was high in brain areas as the thalamus, caudate nucleus, putamen, frontal and temporal cortex, intermediate in the occipital cortrex , cerebellum and low in white matter . The (+)(R) and (-)(S) ^{11}C-nicotine enantiomers showed a similar uptake and pattern of distribution in control brains .

In Alzheimer brains on the other hand, a lower uptake of (+)(R) ^{11}C-nicotine was observed in comparison to (-)(S) ^{11}C-nicotine . The uptake of (-) and especially (+)^{11}C-nicotine to cortical areas was in general lower in Alzheimer patients compared to controls. ^{11}C-butanol, a marker for cerebral blood flow, had a different time course in the brain in comparison with ^{11}C-nicotine and clearly support the assumption that ^{11}C-nicotine has a specific binding profile in brain and that changes in uptake and time course of ^{11}C-nicotine reflect changes in specific binding.

In conclusion ,the pattern of distribution of ^{11}C-nicotine in brain resembles the distribution of nicotinic binding sites. A significant difference in uptake of (-) and (+) ^{11}C-nicotine to the brain is observed in Alzheimer patients compared to healthy volunteers. Further PET studies in man will give valuable information concerning the role and physiological function of the nicotinic receptors subtypes in brain